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## Antenatal Glucocorticoid Treatment: Are We Doing Harm to Term Babies?

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**A**ntenatal glucocorticoids are given to 7–10% of women in Europe and North America at threat of preterm labor. It is undisputed that this therapy significantly reduces neonatal morbidity and mortality in infants born before 34 wk gestation (1, 2). Based on outcomes from multiple clinical trials, current obstetric practice is to administer either a single 2-d course of betamethasone or dexamethasone (*i.e.* two 12-mg doses of betamethasone im at 24-h intervals or four 6-mg doses of dexamethasone im at 12-h intervals) to women in preterm labor between 24 and 34 wk gestation (3). The use of repeat courses of antenatal glucocorticoids is more controversial, although some evidence suggests that a repeat course, if the mother does not deliver but remains at risk of preterm labor, may yield neonatal benefit (2). However, because early clinical diagnosis of preterm labor is difficult and there are no reliable laboratory tests, there are a substantial number of women who receive antenatal glucocorticoid treatment yet subsequently deliver babies at full term, *i.e.* after 37 wk gestation. Little is known about the potential risks or benefits of synthetic glucocorticoid exposure to these infants.

It is now well recognized that exposure to an adverse *in utero* environment during development has long-term effects on physiology and later risk of adult disease (4). Overexposure of the developing fetus to excess glucocorticoids is a key mechanism thought to underlie such “developmental programming” (4). Numerous preclinical studies have shown that administration of dexamethasone to pregnant mothers leads to long-term changes in the offspring, notably permanently altering cardiometabolic and neuropsychiatric functions as well as hypothalamic-pituitary-adrenal (HPA) axis activity (4). The latter may

contribute to some of the broader pathogenesis associated with experimental programming.

Both betamethasone and dexamethasone have high affinity for glucocorticoid receptors but are poor substrates for the placental enzyme 11- $\beta$  hydroxysteroid dehydrogenase type 2, which normally acts as a partial barrier, protecting the fetus from glucocorticoids by breaking down endogenous cortisol into inactive cortisone (4). These synthetic glucocorticoids readily cross the placenta, potentially exposing the fetus to excess glucocorticoids. In animal models, the developing HPA axis appears particularly vulnerable to excess glucocorticoids (4), yet the evidence for detrimental effects of antenatal glucocorticoids on human HPA axis activity has been less clear-cut. This is partly because most studies have included preterm infants, who often have coexisting medical complications and are exposed to stressors and painful procedures while in the neonatal intensive care unit, factors that can *per se* alter HPA axis function (5). Likewise, the type, dose, and timing of administration of glucocorticoid therapy often differ between studies, complicating interpretation. Furthermore, studies have included limited assessments of the offspring HPA axis, often with a single measurement of cortisol levels. Given these caveats, the limited existing data, which include preterm babies in whom the HPA axis may be immature, suggest that among infants exposed to antenatal glucocorticoids, baseline cortisol levels are suppressed during the first postnatal week, and cortisol responses to the painful stress of the heel-stick procedure are suppressed for up to 8 wk (6), suggesting some persistent suppressive effects on HPA axis regulation, but hardly the programming of increased (or reduced) HPA activity seen throughout the lifespan in animal models.

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Abbreviation: HPA, Hypothalamic-pituitary-adrenal.

For article see page 3538

In the article by Alexander *et al.* (7) in this issue of the *JCEM*, the authors report on the first study to examine the impact of antenatal synthetic glucocorticoid exposure on endocrine stress reactivity in term-born children aged 6–10 yr. Maternal stress has itself been implicated as a programming factor (4), and hospitalized women receiving antenatal glucocorticoids are likely to be more worried and “stressed.” Alexander *et al.* (7) therefore introduced an additional control group of stressed mothers who had been admitted to hospital with pregnancy complications but had not received antenatal glucocorticoids. This careful study design goes some way to disentangle the potential confounding effect of maternal stress from the direct effects of antenatal glucocorticoid exposure.

The children exposed to antenatal glucocorticoids were smaller at birth and were born slightly earlier than the control groups; these variables were included as covariates in the statistical analysis. The main finding was that children exposed to antenatal glucocorticoid treatment had significantly increased cortisol reactivity to a standardized laboratory stressor, the Trier Social Stress Test for Children (TSST-C), compared with both control groups. Although these data are the most comprehensive to date, they are still cross-sectional and observational. Prospective data with longitudinal follow-up are necessary to confirm the findings and overcome any possible bias in recruitment/retention. Nevertheless, these findings are consistent with a recent study showing a more pronounced cortisol response to the heel-stick procedure among term infants exposed to betamethasone *in utero*, compared with an unexposed control group (8), and suggest long-lasting effects of antenatal glucocorticoid exposure on HPA axis reactivity. Alexander *et al.* (7) also found that cortisol reactivity to the TSST-C was more pronounced in girls than boys, a finding that is consistent with the sexually dimorphic responses in animal studies where females are generally more susceptible to programming of HPA axis stress responsivity (9). Increased HPA axis activity during the morning diurnal peak has also been reported in children of mothers who voluntarily consumed higher quantities of the 11- $\beta$  hydroxysteroid dehydrogenase type 2 inhibitor licorice in pregnancy (10).

What are the implications of increased HPA axis stress reactivity in these children? From an evolutionary perspective, such an adaptation to an intrauterine insult is thought to be beneficial in the short-term and linked to increased chance of offspring survival in a predicted stressful environment, and hence increased chances of survival to reproductive age (11). However, such adaptations may be detrimental in the longer term. For example, in adult men and women, activation of the HPA axis has been linked to increased risk of cardiovascular risk factors com-

prising the metabolic syndrome including higher glucose, blood pressure, and triglycerides (12), as well as ischemic heart disease, cognitive decline, and depression (12) in later life. Indeed, in preterm infants, antenatal glucocorticoid exposure has been associated with an increase in behavioral disorders at age 3 yr (13), higher systolic and diastolic blood pressures in adolescence (14), and increased insulin resistance, a precursor of type 2 diabetes, at age 30 yr (15). Whether or not the HPA axis hyperactivity observed by Alexander *et al.* (7) contributes to such effects remains to be determined.

There is no doubt that antenatal glucocorticoid treatment for women in preterm labor has benefits for preterm babies, and this justifies the small risk of long-term side effects. Yet with this emerging evidence of potential harm for term infants and no evidence of benefits, it is crucial that we develop ways to accurately identify those women at the greatest risk of preterm labor. Approaches might employ biological markers such as fetal fibronectin as a test of exclusion of preterm labor (16), or the research tool of measurement of cervical length by transvaginal ultrasonography (17). In addition, in 2011, the U.S. Food and Drug Administration approved the use of progesterone supplementation (hydroxyprogesterone caproate) during pregnancy to reduce the risk of recurrent preterm birth in women with a history of at least one prior spontaneous preterm delivery (18). Such strategies may avoid unnecessary glucocorticoid treatment of those women who go on to deliver beyond 37 wk gestation. However, recent Royal College of Obstetrics and Gynaecology guidelines in the United Kingdom recommend routine administration of antenatal glucocorticoids for all women undergoing elective cesarean section at less than 39 wk gestation (19). Although endogenous glucocorticoids rise dramatically in pregnancy, peaking in the third trimester at three times nonpregnant levels (20), the long-term effects of exogenous glucocorticoid exposure in late pregnancy for these children are unknown. A further approach is to consider minimizing the doses of glucocorticoids used. Although Alexander *et al.* (7) observed no differences in childhood cortisol stress responses according to the type of glucocorticoid used, data in a nonhuman primate model suggest dose-associated programming of cardiometabolic parameters by dexamethasone (21), implying that the lowest dose of glucocorticoid possible should be used to minimize long-term adverse effects. This principle is well-established in adult glucocorticoid therapy and might beneficially be incorporated into obstetric thinking as well.

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